Applicants seek to amend claim 7 to include the limitation "while retaining therapeutic activity" to further clarify the invention. Other claim amendments are discussed below in response to the Examiner's rejections.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejection under 35 U.S.C. §112, first paragraph

Applicants respectfully thank the Examiner for withdrawing this ground for rejection.

Rejections under 35 U.S.C. §112, second paragraph

Rejection under 35 U.S.C. §112, second paragraph, withdrawn in-part

Applicants respectfully thank the Examiner for withdrawing, in part, this ground for rejection.

Rejection under 35 U.S.C. §112, second paragraph, maintained in-part

The Examiner has rejected claim 16 as indefinite. While the Examiner has rejected claim *16*, it appears that the Examiner means claim *15*.

Claim 15

After entry of the requested amendment, claim 15 will be directed to "a method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a therapeutically active region of amino acids and a less therapeutically active region of amino acids, comprising: (a) identifying said therapeutically active region of amino acids by structure activity relationship analysis; (b) modifying said peptide at an amino acid included in said less therapeutically active region by coupling thereto a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity; (c) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity, while retaining therapeutic activity of the therapeutic peptide; and (d) analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the

peptide-blood component conjugate has a higher stability than the therapeutic peptide." (Emphasis added).

The Examiner's Rejection

The Examiner alleges that the phrases "therapeutically active region" and "less therapeutically active region" are relative terms. The Examiner argues that the "less therapeutically active region" is relative "[s]ince the therapeutically active region is relative, so is that which is defined by its presence." The Examiner further argues that "what is considered active or less active in one case, may not be so in another case."

Applicants' Response

Without acquiescing to the Examiner's arguments, Applicants request to amend claim 15 to remove any question as to what is meant. Specifically, Applicants request to amend claim 15 to introduce the two following limitations:

- "(a) identifying said therapeutically active region of amino acids by structure activity relationship analysis," and

- "(c) forming a covalent bond ... while retaining therapeutic activity of the therapeutic peptide"

Support for the identification of the therapeutically active region by structure activity relationship (SAR) is found in the description as filed on page 10, line 31 to page 11, line 4 and on page 69, line 30 to page 70, line 4. This amendment merely makes explicit what was already implicit in the claims.

SAR analysis of compounds is used to identify the "therapeutically active region," and is supported in the description as filed on page 11, lines 4-6. Further, SAR analysis allows one of skill in the art to determine precisely what are the numbers and the nature of the amino acids being involved in the therapeutic activity (i.e. binding activity, enzymatic activity, etc).

Support for the retention of the therapeutic activity of the peptide after modification and conjugation is found in the description as filed on page 4, lines 7-16 and on page 70, line 12 to page 71, line 8. Also, a definition for "therapeutic activity" is found on page 11, line 27-28 and is exemplified on page 11, line 28 to page 13, line 9 of the Specification as filed.

Moreover, in order to avoid ambiguity with respect to the expressions "therapeutically active region" and "less therapeutically active region" after entry of the requested amendment, claim 15 will specify that therapeutic activity of the therapeutic peptide is retained after being modified and conjugated to a blood component. If the therapeutic activity is retained, the modification of the peptide has necessarily been made into the less therapeutically active region.

These amendments to claim 15 further clarify the phrase "therapeutically active region" and consequently the expression "less therapeutically active region," and thus define the scope of the claim.

After entry of the requested amendment, this ground for rejection will be moot. Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner has maintained the rejection of claims 7-9, 11-17, and 21-25 under 35 U.S.C. §103(a) as obvious over Pouletty et al. (WO 95/10302) in view of Oppendahl et al. (U.S. Patent No. 5,837,247).

As stated in the prior response and reiterated here, 35 U.S.C. § 103(a) requires that "...differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The prima facie case must satisfy three requirements: 1) the references must teach or suggest all the claim limitations; 2) the prior art combined with general knowledge must include a suggestion or incentive to modify or combine the references; and 3) the modification or combination must have a reasonable chance of success.

Claims 7-9, 11-17, and 21-25

After entry of the requested amendment, both claim 7 and claim 15 will recite "analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide."

After entry of the requested amendment, independent claim 7 will recite "a method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a carboxy terminus and an amino terminus and a carboxy terminal amino acid and an amino terminal amino

acid, comprising: (a) modifying said peptide by coupling a reactive group to the carboxy terminal amino acid, to the amino terminal amino acid, or to an amino acid located between the amino terminal amino acid and the carboxy terminal amino acid; (b) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase degradation, while retaining therapeutic activity of the therapeutic peptide; and (c) analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide."

After entry of the requested amendment, independent claim 15 will recite "a method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a therapeutically active region of amino acids and a less therapeutically active region of amino acids, comprising: (a) identifying said therapeutically active region of amino acids by structure activity relationship analysis; (b) modifying said peptide at an amino acid included in said less therapeutically active region by coupling thereto a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity; (c) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity, while retaining therapeutic activity of the therapeutic peptide; and (d) analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide."

The Examiner's Rejection

The Examiner argues that Pouletty et al. teach the same method steps as that of the instant invention (see the Final Office Action at the end of page 3, at the 3rd paragraph of page 4, and at the last paragraph of page 5). The Examiner further alleges that the preamble does not breadth meaning into the claim. The Examiner also alleges that Pouletty et al. disclose the same method steps as the claims herein.

The Cited References

Pouletty *et al.* teach extending *in vivo* lifetimes of physiologically active agents by associating those agents with longer-lived blood component (Abstract). The reference, however, fails to teach "analyzing the stability of a peptide-blood component conjugate to peptidase

degradation," "confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide," or anything about peptide stability to peptidase degradation.

Oppenhelm *et al.* teaches SEQ ID NO: 1032. The reference, however, fails to disclose a method protecting a therapeutic peptide from peptidase degradation, or a method of coupling a reactive group to a less therapeutically active region.

Applicants' Response

The Examiner fails to satisfy the requirements to establish a *prima facie* case of obviousness for the amended claims on multiple grounds. Specifically, 1) none of the cited references teach or suggest all the claim limitations; 2) the prior art combined with general knowledge fails to include a suggestion or incentive to modify the references; and 3) the references fail to teach that the modification would reasonable chance of success.

First, neither Pouletty et al. and Oppendahl et al. teach or suggest every claim limitation of the amended claims. Specifically, neither reference teaches or suggests a step of "analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide." Pouletty et al. never disclose, suggest, mention, or hint at analyzing the stability of any peptide containing compounds to peptidase degradation. Moreover, Pouletty et al. could not have taught or suggested the step of analyzing the stability of the peptide-blood component conjugate in presence of peptidases, since increased stability to peptidase degradation was not discovered at that time.

In addition, analyzing the stability of the peptides to peptidase degradation greatly improves selection of the claimed peptides over other known methods, including those disclosed by Pouletty et al. The step of "analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide" results in the selection of different, more peptidase-resistant peptide-blood component conjugates than would otherwise be selected. In particular, the selection is a substantial improvement over the methods taught by Pouletty et al., since the methods claimed herein also result in the selection of different, more stable peptide-blood component conjugates than those selected by the methods taught by Pouletty et al. Thus, the additional limitation represents a significant improvement over the methods taught by Pouletty et al.

Oppendahl et al. also lacks the smallest hint of "analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide."

Therefore, Pouletty et al. and Oppendahl et al., either separately or in combination, fail to teach every limitation of the claimed invention as required under 35 U.S.C. §103.

Second, the references, separately or in combination, fail to provide the requisite motivation to combine their teachings to make the claimed invention. Pouletty et al. and Oppendahl et al. are utterly devoid of any motivation to analyze the stability of peptide containing compounds to peptidase degradation, since neither reference teaches, suggests, mentions, or hints at peptidase degradation in the first place. Furthermore, as pointed out above, the stability of the peptides to peptidase degradation results in the improved selection of peptides over other methods, particularly the methods taught by Pouletty et al. Even though the teachings of the cited references could be modified, the references must still have suggested the modification.

Third, the cited references, either separately or in combination, provide no reasonable expectation that the modification will succeed. In the present invention, it has been surprisingly discovered that a conformational rearrangement is responsible for the high stability of a peptide toward peptidase degradation after modification and conjugation of the peptide to a blood component. The cited references are both devoid of any suggestion of peptidase degradation. Further, there is no suggestion or mention that one skilled in the art would succeed in analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide. The cited references certainly fail to show the surprisingly improved selection of peptides observed by the instant invention.

In view of the foregoing, the proposed amendment of claims 7 and 15 are therefore not obvious over the cited references. Applicants respectfully request that the rejection be withdrawn after entry of the requested amendment.

Conclusion

In light of the above amendments and remarks, Applicant believes that this case will be in condition for allowance after entry of the requested amendment. Should there be any remaining issues that remain unresolved, the Office is encouraged to telephone the undersigned.

Attached hereto is a marked up version showing the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made.**" A deleted item is indicated by crossing out the item, e.g., ~~and~~, while an insertion is underlined.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 500862002300. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: February 24, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

7. (Thrice Amended) A method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a carboxy terminus and an amino terminus and a carboxy terminal amino acid and an amino terminal amino acid, comprising:

(a) modifying said peptide by coupling a reactive group to the carboxy terminal amino acid, to the amino terminal amino acid, or to an amino acid located between the amino terminal amino acid and the carboxy terminal amino acid; ~~and~~

(b) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase degradation, while retaining therapeutic activity of the therapeutic peptide; and

(c) analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide.

8. (Reiterated) A method according to claim 7, wherein the peptide-blood component conjugate is formed *in vivo*.

9. (Reiterated) A method according to claim 7, wherein the peptide-blood component conjugate is formed *ex vivo*.

11. (Reiterated) A method according to claim 7, wherein said reactive group comprises a maleimide group.

12. (Reiterated) A method according to claim 7, wherein said reactive group is coupled to said peptide via a lysine and/or a linking group.

13. (Reiterated) A method according to claim 7, wherein said blood component is albumin.

14. (Reiterated) A method according to claim 7, wherein one or more of said amino acids is synthetic.

15. (Thrice Amended) A method for protecting from peptidase degradation a therapeutic peptide sensitive to such peptidase degradation *in vivo*, said peptide comprising between 3 and 50 amino acids and having a therapeutically active region of amino acids and a less therapeutically active region of amino acids, comprising:

(a) identifying said therapeutically active region of amino acids by structure activity relationship analysis;

(b) modifying said peptide at an amino acid included in said less therapeutically active region by coupling thereto a reactive group to said amino acid to form a modified peptide, such that said modified peptide has therapeutic activity; ~~and~~

(c) forming a covalent bond between said reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity, while retaining therapeutic activity of the therapeutic peptide; and

(d) analyzing the stability of said peptide-blood component conjugate to peptidase degradation and confirming that the peptide-blood component conjugate has a higher stability than the therapeutic peptide.

16. (Reiterated) A method according to claim 15, wherein the peptide-blood component conjugate is formed *in vivo*.

17. (Reiterated) A method according to claim 15, wherein the peptide-blood component conjugate is formed *ex vivo*.

21. (Reiterated) A method according to claim 15, wherein said peptide has a carboxy terminus, an amino terminus, a carboxy terminal amino acid and an amino terminal amino acid, and wherein step (b) further comprises:

(a) if said less therapeutically active region is located at the carboxy terminus of said peptide, then modifying said peptide at the carboxy terminal amino acid of said peptide; or

(b) if said less therapeutically active region is located at the amino terminus of said peptide, then modifying said peptide at the amino terminal amino acid of said peptide; or

(c) if said less therapeutically active region is located at neither the amino terminus nor the carboxy terminus of said peptide, then modifying said peptide at an amino acid located between the carboxy terminus and the amino terminus.

22. (Reiterated) A method according to claim 15, wherein said reactive group is a maleimide group.

23. (Reiterated) A method according to claim 15, wherein said reactive group is coupled to said peptide via a linking group.

24. (Reiterated) A method according to claim 15, wherein said blood component is albumin.

25. (Reiterated) A method according to claim 15, wherein one or more of said amino acids is synthetic.